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Two Global Methods for Molecular Geometry Optimization

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TWO GLOBAL METHODS FOR MOLECULAR GEOMETRY OPTIMIZATION

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Abstract : The determination of molecular conformations, based on energy minimization, has to overcome the presence of multiple minima in the energy surface. Thus, the need to reckon on efficient global optimization methods. Here, we are concerned with two models: one for peptide molecules that takes into account Lennard-Jones (L-J), hydrogen bonding, electrostatics and torsional terms, and another for atomic clusters that only considers L-J potentials. We discuss our experience when solving these models with global optimization methods different in nature: the exponential tunneling algorithm, which is deterministic, and stochastic procedures based on the simulated annealing concept. These methods have found improved conformations for atomic clusters and for small peptide molecules, respectively, and, as such, they appear as suitable tools in this context.

Keywords : molecular conformation, peptide molecules, small atomic clusters, global optimization, simulated annealing, tunneling algorithms.

DEUX METHODES GLOBALES POUR L'OPTIMISATION DE GEOMETRIES MOLECULAIRES

Résumé : Pour déterminer la structure moléculaire obtenue par minimisation de l'énergie, il faut surmonter le problème de la présence de minima multiples sur la surface d'énergie. Il est donc nécessaire de recourir à des méthodes numériques d'optimisation globale efficaces. Nous considérons deux modèles de structures moléculaires : l'un représente la conformation des molécules de peptides qui prend en compte le potentiel de Lennard-Jones (L-J), les liaisons d'hydrogène, les termes électrostatiques et les termes de torsion; l'autre modélise les clusters atomiques qui prennent seulement en compte le potentiel de L-J. Nous présentons l'expérience que nous avons acquise en résolvant ces modèles avec des méthodes d'optimisation globale qui sont très différentes de nature : la méthode des tunnels exponentielle, qui est déterministe , et des procédures stochastiques qui sont à la base du concept de recuit simulé. Ces méthodes ont trouvé de meilleures conformations pour les clusters atomiques et pour les petites molécules de peptides. Elles apparaissent donc comme des outils appropriés pour ce genre de problèmes.

Mots clés : conformation moléculaire, molécules de peptides, petits clusters atomiques, optimisation globale, recuit simulé, méthode des tunnels.

1. Introduction

Mathematical models are often used to describe chemical processes. One of the most challenging problems is the determination of molecular conformations through energy minimization, the main difficulty being the enormous amount of local minima in the energy surface. In order to choose the appropiate method to find out minimum energy geometries, one has to consider the mathematical characteristics of the models used. We present here two global optimization methods, simulated annealing (SA) and the tunneling algorithm (TA), that have been successful in determining minimum energy conformations for small peptide molecules and atomic clusters. In section 2, after a brief presentation of the model for minimum energy conformation of peptides, we describe some results obtained with procedures that incorporate the SA concept. Section 3 is devoted to the TA and its application to the atomic cluster conformation problem. A summary of our experience is reported.

2. Peptide conformation through simulated annealing

In the realm of protein research, the variety of numerical optimization techniques proposed to locate molecular structures with minimum potential energy, goes from Bremermann's method[1] to Monte-Carlo minimization[2], and includes variations of the powerful technique known as simulated annealing (SA)[3-6]. Since its inception[7], SA has proved to be an adequate tool to deal with many difficult combinatorial optimization problems[8-10].

A peptide molecule can be modelled as a mobile graph[4], where the nodes and the edges correspond, respectively, to the constituent atoms and to the atomic links between the atoms. Let Ω denote the set of integer values going from -180 to $+180$. Considering bond distances (atomic links) and bond angles (the angles between two adjacent atomic links) as fixed, the 3-dimensional shape of this graph is determined by $\Theta = (\theta_1, \ldots, \theta_n) \in \Omega^n$, where the θ_i are the values of the *dihedral* angles of both the main chain and the lateral chains. The potential energy $E(\Theta)$ of the corresponding molecule might be evaluated by means of ECEPP/2[11], which is an empirical, pair interaction function, made up of Lennard-Jones, hydrogen bonding, electrostatics and torsional terms.

With this model on hand, the peptide conformational problem can be stated as that of finding $\Theta^* \in \Omega^n$ such that $E(\Theta^*) \leq E(\Theta)$, for any $\Theta \in \Omega^n$. In view of the huge, unknown number of local minima of $E(\Theta)$, the latter problem seems to be at least as difficult as the combinatorial optimization problems belonging to the *NP-complete* class, i.e., those problems for which all known algorithms that are able to solve them require a number of steps that grows exponentially with the number of variables, and for which there is little hope to ever find a polynomial solution algorithm.

A general SA procedure for this problem is now described. To every $\Theta \in \Omega^n$ associate a

neighborhood $H(\Theta) \subset \Omega^n$ as the set of all conformations obtainable from Θ by arbitrarily modifying the value of one dihedral angle. SA starts with any conformation and with a nonnegative parameter T (called *temperature*) set to an appropiate high value. Given $\Theta \in \Omega^n$, a neighbor $\Theta' \in H(\Theta)$ is randomly generated with a uniform probability distribution. If $\Delta := E(\Theta') - E(\Theta)$ satisfies an *accepting rule*, then Θ' becomes the new current conformation, otherwise Θ' is rejected. The process is iterated until a condition of *steady state* is attained, in which case T is lowered according to a *cooling strategy* and the whole process is started anew. The algorithm halts when a *stop criterion* is satisfied: a local minimum with respect to $H(\Theta)$ has been reached. The most commonly used accepting rule is: Θ' is accepted if either $\Delta < 0$ or $x \leq \exp(-\Delta/T)$ (x is a random number uniformly distributed in $[0, 1]$). Instead, in a variation known as *threshold accepting*[12] the rule states that Θ' is accepted if $\Delta < T$.

In [4-5] experimentation with SA derived procedures to locate minimum energy conformations of peptides with up to 24 dihedral angles (N-acetyl-N'-mehtyl-glycineamide, N-acetyl-N'-methyl-alanineamide, N-acetyl-N'-methyl-aspartic acid, pentaglycine, Met^5-enkephalin, and Leu^5-enkephalin) was reported. To our knowledge, the obtained SA structures are the lowest available. Moreover, the threshold accepting version as compared with the classical one, is simpler, requires less computing effort, and produces conformations with lower energy. With the largest peptides considered (24 dihedral angles), around 300,000 objective function evaluations were needed. This fact prevented to try bigger sizes, mainly because every evaluation was expensive in computing time. However, this drawback might be reduced through a more efficient implementation of the objective function evaluation.

SA procedures are easy to understand and require small effort in computer implementation. Complex objective functions, like ECEPP/2, do not prevent their use at all. Experiments can be performed in order to appropiately select the neighborhood, the cooling strategy, the steady state condition and the stop criterion. For instance, the best results are obtained when the neighborhood size is gradually reduced during the search process. Another useful device is to allow increases of T during the process whenever the remaining time for a run is large enough. In conclusion, SA seems to be an appropiate tool to conduct further research in molecular geometry optimizations with a high degree of confidence.

3. The tunneling method and atomic clusters

The name of the method, describes its aim: to tunnel from one valley of the objective function to another, to find a sequence of local minima with decreasing values. There are two phases in the method: in phase 1, from a given initial point x^0, a local minimum (LM) x^* with $f^* = f(x^*)$ is found, using any local optimization method. From x^*, phase 2 obtains a point x^0 in another valley with $f(x^0) \leq f^*$, which in turn will serve as initial point for phase 1. The problem in phase 2 can be reformulated as the problem of finding

x^o such that

$$T_c(x^o) = \frac{f(x^o) - f^*}{\| x^o - x^* \|^{2\lambda^*}} \leq 0$$

or the more convenient problem of finding x^o such that [14]

$$T_e(x^o) = (f(x^o) - f^*) \exp(\frac{\lambda^*}{\| x^o - x^* \|^2}) \leq 0$$

The function T_c is called the *classical*[13] tunneling function (CTF) and T_e the *exponential*[14] tunneling function(ETF). These functions have a pole placed at $x^*$with strength λ^* (for the CTF λ^* is an integer that depends on the multiplicity of the minimum). To find x^o with $f(x^o) \leq f^*$ we can now use a local descent method. We have then found a point in another valley.

What we have just described is the main idea, but the algorithm has to deal with special features of different objective functions, and we will mention here the most important ones.

1. In practice T_c, or T_e, inherits the critical point behaviour of the original function f, and in spite of the fact that $T(x)$ is positive (otherwise we have the solution x^0), a gradient type local descent search would be trapped at those critical points. To deal with this difficulty we can use the fact that increasing the strength parameter λ has a smoothing effect. Then by multiplying $T(x)$ by a term called a *mobile pole* : $\frac{1}{\|x^o - x^m\|^{2\lambda_m}}$ or $\exp(\frac{\lambda^m}{\|x^o - x^m\|^2}) \leq 0$ that the algorithm will automatically turn off ($\lambda^m = 0$) when $T(x)$ is smooth, or increase it ($\lambda^m = \lambda^m + \Delta\lambda$) to get a descent direction if it gets near a critical point, we locally smooth the problem.

2. For some objective functions f, the tunneling method might find many local minima at the same level f^*. This is expensive and in some applications these local minima are not of any particular interest. In this case the algorithm can be easily modified to find x^0 satisfying $T(x^o) \leq -\epsilon$, to some desired tolerance ϵ.

3. In order to avoid going back to local minima already found at the same level, it suffices to multiply in T_c or T_e by terms that make the previous local minima poles.

4. An interesting comment here, is that if x^* is the global solution, then x^0 does not exist. Numerical experiments have shown that the global minimum is usually obtained with less than 20% of the total computing time, the other 80% being used to check that the candidate is indeed a global minimum. Given a candidate x^* the stopping test searches for x^0, starting from $2n$ different *neighbor points* generated using the cartesian directions (as in the SA method) i.e., $x_i = x^* + \epsilon r_i$, where r_i is the ith unitary vector (positive for the first n directions and negative for the remaining n), and $\epsilon << 1$. If after these $2n$ searches the method fails to find x^0, it stops. The best local minimum found so far is then said to be a good candidate to be the global minimum. Random directions can also be used if more than $2n$ searches are allowed,

i.e. if the cost of the search permits it. In some applications, where getting minima with the value of the objective function less than a certain threshold is the aim, the expensive stopping rule can be avoided.

This method in its present form, can only be used when gradient information is available and the function is C^2. It only handles continuous variables and it has also been implemented to deal with bounds [14]. The general constrained case has also been studied[15,16], and the method has been adapted to deal with least squares problems with singular jacobians (with rank n-1)[17,18]. The reader is refered to a general review[19]. The method is cheap, because it ignores all minima above the current local optimal level, and because it is not based on sampling, the number of function evaluations is generally small. Thus, it is especially suited for either expensive objective functions or functions with a large number of local minima (there are reported results with problems having 10^8 local minima[19]). The tunneling algorithm has been successfully applied to the problem of determining the structures of atomic clusters with minimum Lennard-Jones potential energy. Suppose the cluster conformation of n atoms is given by the cartesian coordinates $p_i = \{x_i, y_i, z_i\}$, $i = 1, \ldots, n$. The simplest assumption about interaction energy is that of Lennard-Jones two-body forces between atoms

$$V_n(p) = \sum_{i=1}^{n-1} \sum_{j>i}^{n} v(\| p_j - p_i \|_2).$$

where $v(r) = r^{-12} - 2r^{-6}$ is the potential energy of two atoms at a distance r from each other (the minimum of v for two atoms occurs when $r = 2^{1/6}$). Under this assumption, the atomic cluster conformation problem is then that of finding p^* such that $V_n(p^*)$ is minimal.

In order to choose an optimization method to solve this problem, the characteristics of the energy function V_n should be taken into account. We note first that V is continuous, differentiable and computationally very cheap to evaluate. The number of local minima is unknown and grows exponentialy with the number n of atoms in the cluster[20]. Moreover, and because of symmetries and relabelling, there is a multiplicity of local minima with the same energy level. The tunneling method can deal with this problem as explained before.

Ideally, the problem would be solved by a local minimizer that starts its iterations from any conformation lying in the valley of a global optimum. As, in general, there is not known method to determine such conformation, most reported results come from local minimizers coupled with physical intuition that provides the initial conformations. Another approach is that of using a global optimizer, able to pass from one valley to another, and, hopefully at the end, to a global optimum valley. Thus, the tunneling algorithm appears suitable to deal with the atomic cluster conformation problem.

Clusters of up to 72 atoms confined to a plane were studied[14]. From arbitrary initial conformations, the tunneling algorithm succeeded in finding solutions with atoms positioned at grid points corresponding to a hexagonal lattice packing, as predicted by other authors[21].

As expected, for $n = 7$ six atoms were positioned at the vertices of a regular hexagon of side size $r^* = 2^{1/6}$ plus one atom at its center. This shape can also be viewed as six equilateral triangles placed side by side. Clearly, 24 equal size equilateral triangles can be placed so as to form a regular hexagon of side size $2r^*$, and then 19 atoms can be positioned at the vertices of triangles in order to get a good candidate for optimality, compact conformation. The tunneling algorithm showed that this conformation is not optimal for $n = 19$, and the optimization process compressed it slightly distorting the inside triangles. This phenomenon was observed in every cluster of size $n \geq 19$ under study.

Several papers have been devoted to the 3-dimensional model[22-27]. The best reported results for small size clusters ($n \leq 147$) have been obtained with either SA techniques[25-26] or local optimization methods whose initial conformations follow an icosahedral growth scheme[27]. With one exception ($n = 38$), all these solutions were also obtained by the tunneling method[28], which starting from arbitrary initial points, passed from one valley of the energy function to another until it could not improve the energy value in the allowed time. To give an idea of the computational cost, for 8 atoms (24 optimization variables), starting at a random intial point, the method made 10570 function evaluations[28]. Comparing with the cost of the SA method reported in last section for 24 dihedral angles, TA is much cheaper, at the price of the uncertainty of being at the global minimum. In the case of the 38 atoms cluster the tunneling algorithm found a conformation with lower Lennard-Jones potential energy than any other proposed elsewhere. This result is remarkable not only as a counterexample for the generally accepted icosahedral sequence proposed by Northby[27], but also because the obtained cluster shape corresponds to that of the *tetrakaidecahedron*, a beautiful semi-regular polyhedron studied by Archimedes in the third century B.C., and reported to be present in some crystals[29].

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